Journal of Nephrology and Kidney Diseases
Volume 5 | Issue 1
ISSN: 2767-9225

Research Article Open Access

Circulating Inflammatory Cytokines and Acute Kidney Injury: a Bidirectional Two-Sample Mendelian Randomization Study

Hanjing Zhou, Jun Ying, Jian Huang*

[1]Department of Nephrology, Jinhua Hospital of Zhejiang University, 365 Renmin East Ave, Jinhua 321000, Zhejiang, China

***Corresponding Author**: Jian Huang, Department of Nephrology, Jinhua Hospital of Zhejiang University, 365 Renmin East Ave, Jinhua 321000, Zhejiang, China, E-mail: zjjhzxyyhj@163.com

Citation: Hanjing Zhou, Jun Ying, Jian Huang (2024) Circulating Inflammatory Cytokines and Acute Kidney Injury: a Bidirectional Two-Sample Mendelian Randomization Study, J Nephrol Kidney Dis 5(1): 105

Received Date: June 11, 2024 **Accepted Date:** July 11, 2024 **Published Date:** July 15, 2024

Abstract

Acute kidney injury (AKI) formerly known as acute kidney failure, is a global public health concern. Although closely related to the inflammatory response, with multiple inflammatory factors involved in the development and occurrence of AKI, the pathogenesis of AKI remains unclear. In this study, we investigate the causal relationship between circulating inflammatory cytokines and AKI through bidirectional Mendelian randomization (MR) analysis. Data on circulating inflammatory cytokines and AKI were selected from the Genome-Wide Association Study database, and 91 circulating inflammatory cytokines were compared with the outcome data from two different databases (FinnGen R10 and UKB). The inverse-variance weighted method, MR-Egger regression, and the weighted median estimator were used for MR analysis, Cochran's Q test was used to test the heterogeneity of the results, and sensitivity analysis was performed to verify the reliability. Subsequently, meta-analysis was conducted on the main outcomes of the inverse-variance weighted analysis, with multiple corrections performed on all results to obtain positive results. Finally, we conducted reverse causal verification of the positive inflammatory cytokines and outcomes. We found a causal relationship between the inflammatory cytokine GCST90274790 (fibroblast growth factor 5, FGF5) and AKI (OR = 0.921, 95% CI: 0.881–0.962, P = 0.000226)). Two-sample MR was performed again using AKI as the exposure variable and FGF5 as the outcome variable, and no reverse causality was observed. The results show that FGF5 is involved in the occurrence and development of AKI and may be a protective factor against AKI progression. This study provides new insights into cytokine mediators in AKI, as well as promising future research directions.

Keywords: Acute Kidney Injury; Circulating Inflammatory Cytokines; Bidirectional Mendelian Randomization; Cytokine Mediator; Causal Relationship; Pathogenesis

Introduction

Acute kidney injury (AKI) is a clinical syndrome characterized by a dramatic decline in kidney function that occurs over a short period of time and manifests as increased levels of urea nitrogen and creatinine in the blood, as well as decreased urine output [1]. AKI is a global public health challenge with diverse impacts; it affects approximately 13% of hospitalized patients worldwide, with a higher proportion in intensive care units [2, 3, 4], and exhibits poor prognosis, with approximately 50% of patients eventually progressing to end-stage renal failure [5]. AKI incidence may be even higher in developing countries owing to limited medical resources, infection prevalence, and the inappropriate use of nephrotoxic drugs. The causes of AKI vary and can be divided into three categories: prerenal, renal, and post-renal. AKI caused by prerenal azotemia or acute tubular necrosis accounts for approximately 75% of all AKI events [6]. The common risk factors for AKI include sepsis, cardiogenic shock, acute heart failure, surgery, trauma, nephrotoxic drugs, contrast agents, and chronic kidney disease [7, 8]. AKI increases both short and long-term mortality and may promote the development of chronic kidney disease [9, 10, 11].

Currently, effective treatments for AKI are lacking, with no specific drugs available to alleviate kidney damage . Existing treatments include correcting the cause of AKI, maintaining electrolyte balance, controlling blood pressure, and, if necessary, performing renal replacement therapy[12] . However, according to evidence-based medical research, the prognosis of patients with AKI is not improved regardless of early or late dialysis treatment time or the choice of dialysis method [13, 14].

Moreover, in high-risk settings, drug treatment for AKI is often limited by late diagnosis, heterogeneous syndromes, variable clinical manifestations, and complex pathophysiology. Therefore, the pathogenesis and potential therapeutic targets of AKI require urgent clarification.

Although the pathogenesis of AKI remains unclear, its occurrence and development are likely related to inflammation, immune disorders, oxidative stress, apoptosis, and mitochondrial dysfunction . Pathologically, AKI is characterized by severe or even fatal damage to renal tubule cells, apoptotic necrosis, and subsequent renal dysfunction [15, 16]. Renal inflammation is characterized by a complex network of interactions between renal parenchymal cells and innate immune cells, accompanied by the chemotaxis and aggregation of circulating monocytes, lymphocytes, and neutrophils, as well as the release of inflammatory mediators that mediate adaptive responses and tissue repair [17, 18, 19]. Tubular epithelial cells, which represent the highest proportion of innate cell types in the kidney, are not only the target cells of kidney injury, but also involved in driving inflammation [20]. In response to various stresses and injuries, such as ischemia-reperfusion, proteinuria, nephrotoxin, and metabolic disorders, tubular epithelial cells can transform into a secretory phenotype then produce and release various bioactive molecules (such as chemokine MCP-1), promoting the recruitment of inflammatory cells such as macrophages, the activation of fibroblasts, and the loss of endothelial cells . This eventually leads to

tubulo-interstitial inflammation and fibrosis [21, 22]. Tubular necrotizing inflammation is a positive feedback loop between renal tubular cell death and interstitial inflammation, which can aggravate kidney injury [23]. However, renal tubular epithelial cells exhibit immune properties and can widely express toll-like receptors, NOD-like receptors (NLRs), and the NLRP3 inflammasome, which play an important role in the pathological process of various renal diseases, such as obstructive nephropathy and ischemia-reperfusion injury [24].

Indeed, various inflammatory cytokines are involved in AKI development ; however, the exact causal mechanism remains unclear. Therefore, identifying the key regulatory factors of renal inflammation that contribute to the prevention and treatment of various types of nephropathy has great clinical significance.

Mendelian randomization (MR) studies, which use genetic variants as instrumental variables, provide a unique approach for reducing the influence of confounding factors, avoiding causal confounding factors, and obtaining direct evidence of the causal

relationships between exposure factors and disease outcomes [25, 26]. This approach not only helps uncover potential biological mechanisms and therapeutic targets but also serves as a cost-effective alternative in situations where randomized controlled trials are ethically or practically difficult to perform. The application of MR enhances the robustness of research and has important scientific and practical implications for public health policymaking and the development of new treatments. However, MR applications in the field of AKI remain limited. The integration and application of multi-omics data will substantially improve the breadth of research in this field.

Therefore, in this study, we explore the causal relationship between inflammatory cytokines and AKI using MR. We employed genetic techniques as a surrogate for inflammatory cytokines to investigate the potential causal and consequential involvement of inflammation in the progression of AKI.Revealing the causal pathways will offer enhanced understanding of biological mechanisms and novel therapeutic targets for AKI intervention.

Method

Data Sources

Genetic data on inflammatory cytokines and AKI were obtained from summary statistics of large-scale genome-wide association studies (GWAS) or meta-analyses of GWAS, then used to estimate genetic associations and perform MR. In total, 91 circulating inflammatory cytokines were derived from a meta-analysis of 11 cohorts with 14,824 participants of European ancestry. The original publication provides a detailed description of the methods used to measure inflammatory proteins [27].

AKI data were obtained from the United Kingdom Biobank (UKB) and FinnGen cohorts. The UKB is a population-based cohort study involving over half a million

UK residents aged 40–69 years, recruited from 2006 to 2010.This data comes from the Pan-UKB team and is available at https://pan.ukbb.broadinstitute.org. FinnGen includes more than 220,000 hospitalized patients of European ancestry, which enriched the disease endpoints [28]. We extracted clinical and genetic data from the 420,531 participants (7,727 patients with AKI and 412,804 controls) of the UKB cohort, as well as summary statistics from 403,135 participants (6,429 patients with AKI and 396706 controls) of the FinnGen cohort. As all data are already in the public domain, no additional ethical approval was required for this study.

Single Nucleotide Polymorphism Selection

Genetic instruments comprise one or more genetic variants and exhibit properties that enable their use as instrumental variables in MR studies. Here, single nucleotide polymorphisms (SNPs) were used as instrumental variables to derive the causal relationships between exposure and outcome variables. Three basic assumptions should be met for the selection of instrumental variables. 1) Association hypothesis: the selected SNPs must be significantly associated with exposure ($P < 5\times10^{-8}$). 2) Independence assumption: SNPs must be independent of confounders and have no pleiotropic association with them. 3) Exclusivity hypothesis: SNPs can only affect the outcomes by influencing the exposure factors and cannot affect the outcomes in other ways.

First, inflammatory cytokines with $P < 1\times^{10-5}$ were retained and the F-statistic, an important indicator for measuring the strength of SNPs as instrumental variables, was calculated using the (Beta/SE)2 formula, where Beta represents the regression coefficient and SE represents the standard error. F > 10 generally indicates a strong instrumental variable, implying a strong association between the variant and inflammatory cytokines and providing a reliable basis for causal inference. The

F-values are provided in supplementary table 1. Second, the minimum allele frequency threshold was set above 0.01 to eliminate the potential interference of rare variants on the results and to ensure that the analyzed SNPs were more common in the

population, thereby increasing the statistical power and representativeness of the study. Finally, linkage disequilibrium was removed to reduce redundancy and overfitting in the analysis by setting the following parameters: clump_kb = 10,000 and clump_r2 =

0.001. This ensures that, when the correlation coefficient between two SNPs is less than 0.001 within a range of 10,000 kilobast pairs, these SNPs are treated as independent variants, which avoids the influence of SNPs exhibiting high linkage disequilibrium on the results. The comprehensive application of these strategies not only enhances the robustness of MR analysis but also provides strong scientific support for revealing the causal relationship between genetic variation and disease risk, which in turn provides an important genetic basis for the development of disease prevention, diagnosis, and treatment strategies.

Table 1: MR results of Acute kidney injury on FGF5

Database	SNPs	Methods	SE	*P* value	OR	95%CI
		Inverse variance weighted	0.04208	0.38322	0.96396	0.88763-1.04685
Finngen R10	14	MR Egger	0.10065	0.10065	1.04386	0.85696-1.27152
		Weighted median	0.05792	0.07118	0.90075	0.80408-1.00906
		Inverse variance weighted	0.03801	0.123476	0.94312	0.87541-1.01608
UKB	20	MR Egger	0.09937	0.06135	0.82012	0.67498-0.99648
		Weighted median	0.05250	0.12639	0.92288	0.83264-1.02291

MR, Mendelian randomization; SE, standard error; OR, odds ratio; SNPs, single-nucleotide polymorphisms;CI, confidence interval;

Statistical Analysis

Data with less than three SNPs were excluded from the exposure data, whereas data corresponding to SNPs in the outcome and exposure data were retained. The data were then culled for palindromic SNPs with parameter action = 2, followed by data culling for exposure data with mr_keep false.

An MR-PRESSO analysis was performed on the processed data to remove outliers. Before MR-PRESSO, the data were tested for horizontal pleiotropy, and the outliers were removed from the data with horizontal pleiotropy. The MR-PRESSO criteria were NbDistribution = 3,000 and SignifThreshold = 0.05.

MR analysis was performed on exposure data after the above treatments and on AKI data from two different outcome databases using various methods, which included the inverse-variance weighted (IVW), MR-Egger, and weighted median methods. MR Results are presented in supplementary table 2. The data were tested for heterogeneity prior to MR analysis; the fixed-effects IVW model was used for data with heterogeneity and the random-effects IVW model was used in all other cases.

Meta-analysis was then performed on the IVW results, the results are presented in supplementary table 3. After meta-analysis, multiple corrections were performed on the results using Bonferroni correction and false discovery rate (FDR) correction. The final results were considered positive if $P < 0.05$, the beta value direction of the other methods was consistent, and no horizontal pleiotropy was observed.

Sensitivity Analysis

Cochran's Q test was used to test for heterogeneity, where P > 0.05 indicated no heterogeneity(supplementary table 4). Pleiotropy refers to the potential effect of an instrumental variable on the outcome (AKI) through biological pathways unrelated to the exposure factor. The MR-Egger test was used to test for horizontal pleiotropy, with P > 0.05 indicating no horizontal pleiotropy. The MR-PRESSO Globel test was also used to test for horizontal pleiotropy, with NbDistribution = 3,000 and P > 0.05 indicating no horizontal pleiotropy（supplementary table 5）. Estimates of the causal associations can be adjusted to exclude outliers.

All analyses were performed using the "Two-Sample MR" and "MR-PRESSO" packages in R version 4.2.1. In addition, the results were interpreted using β values and the corresponding 95% confidence interval (CI), where P < 0.05 was considered statistically significant.

Results

Causal Effect of Inflammatory Cytokines on AKI

The results suggested a causal relationship between the inflammatory cytokine GCST90274790 (fibroblast growth factor 5 (FGF5)) and AKI. Scatter plots of data from the two different databases showed a negative correlation (Figures 1 and 2). A forest plot of the final positive results after correction in the meta-analysis is shown in Figure 3. The meta-analysis showed that FGF5 significantly reduced the risk of AKI (OR = 0.921, 95% CI: 0.881–0.962, P = 0.000226).

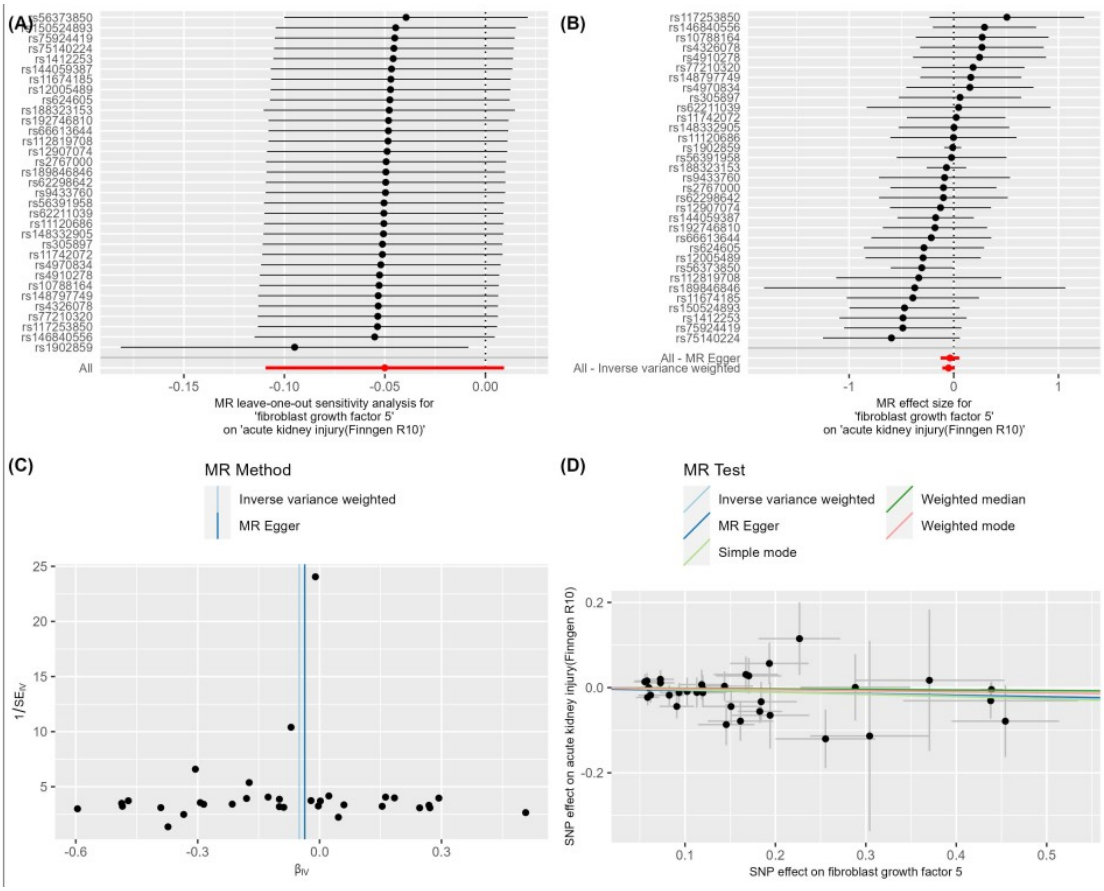

Figure 1: Combined plot showing the Mendelian randomization results of GCST90274790 (FGF5) on AKI using data from FinnGen R10: (A) leave-one-out sensitivity analysis; (B) forest plot; (C) funnel plot; (D) scatter plot.

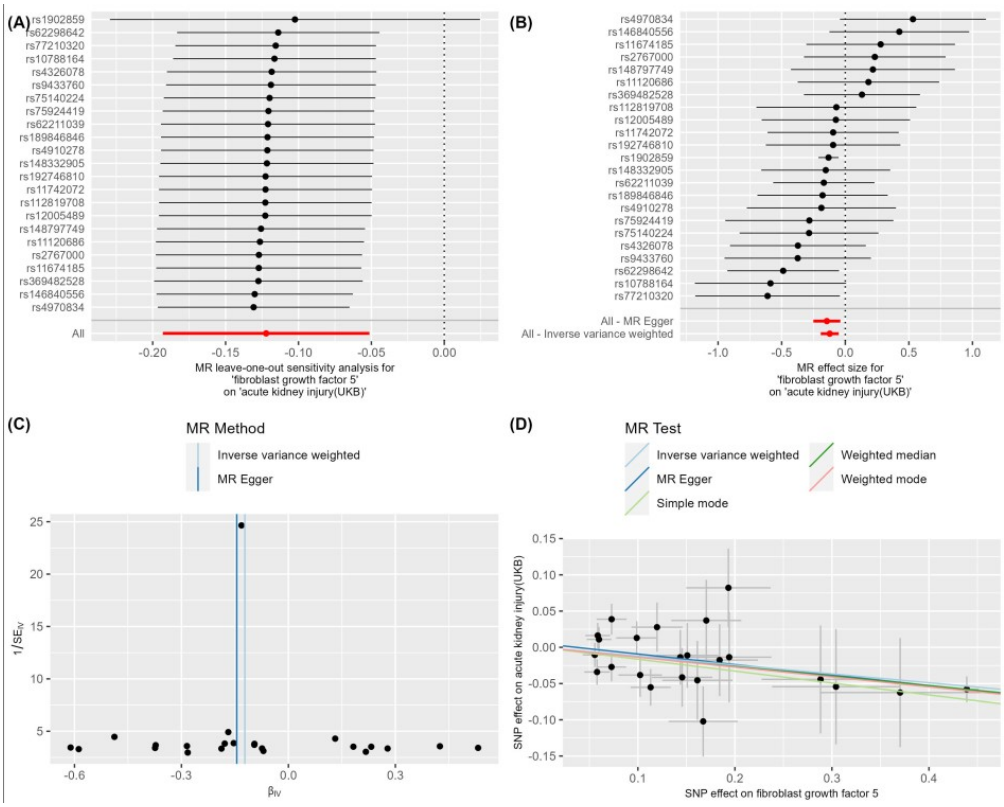

Figure 2: Combined plot showing the Mendelian randomization results of GCST90274790 (FGF5) on AKI using data from UKB: (A) leave-one-out sensitivity analysis; (B)forest plot; (C) funnel plot; (D) scatter plot.

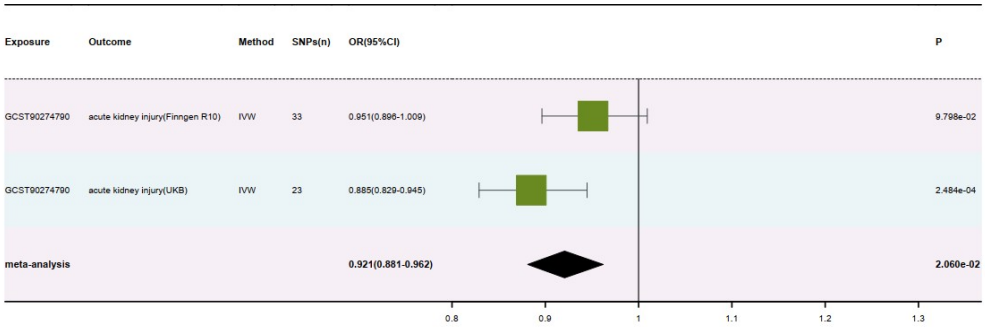

Figure 3: Forest plot showing the meta-analysis of Mendelian randomization performed on the inverse-variance weighted results for FGF5 in AKI.

No Causal Effect of AKI on Inflammatory Cytokines

Two-sample MR was performed again using AKI as the exposure variable and FGF5 as the outcome variable. The results indicated no reverse causality, as shown in Table 1.

Discussion

We explored the causal relationship between 91 inflammatory cytokines and AKI using MR, combining meta-analysis and FDR correction to increase the consistency and accuracy of the results. The results showed that FGF5 is involved in the development of AKI and is a protective factor, with FGF5 overexpression protecting against AKI. Elevated serum levels of FGF5 in patients with AKI often predict a better prognosis . Therefore, we identified FGF5 as an effective therapeutic and prognostic target for AKI.

FGF5 is a member of the fibroblast growth factor family, which has at least 23 known members. FGF5 participates in a series of important physiological and pathological processes, including angiogenesis, injury repair, embryonic development, and endocrine regulation in a paracrine or endocrine manner [29]. FGF family members exert their effects by interacting with distinct FGF receptors located on the cellular membrane, thereby initiating downstream signaling cascades responsible for modulating cellular behavior[30]. Recent studies in both clinical and biological fields have provided evidence that the signaling pathway of FGF has a significant impact on maintaining the balance of phosphate/vitamin D, cholesterol/bile acid, and glucose/lipid metabolism. FGF signaling plays an important role in tissue repair and regeneration mechanisms. Furthermore, this signaling pathway has been found to contribute significantly to the treatment of various human diseases including congenital craniosynostosis, osteoarthritis, chronic kidney disease, cardiovascular disease, dwarfism, hypophosphatemia, obesity, insulin resistance, as well as certain types of cancers[31, 32].

Although FGF5 protects against AKI, its exact mechanism of action remains unclear. We hypothesize that FGF5 plays a protective role in AKI by inhibiting the release of proinflammatory factors, reducing oxidative stress, and alleviating renal tubular epithelial cell damage through certain signaling pathways. Hao X et al. demonstrated that FGF5 attenuates cardiomyocyte pyroptosis through inhibition of CaMKII/NFkB signaling and activation of NLRP3, caspase-1, IL-1b, and IL-18, thereby protecting the heart from septic injury [33]. Zhang et al. suggested that downregulation of

miR-145-5p reduces the levels of proinflammatory cytokines, including tumor necrosis factor-α, IL-6, and improves the survival of retinal ganglion cells, thereby

delaying the progression of diabetic retinopathy by targeting FGF5 [34]. Furthermore, Li et al. demonstrated that FGF5 can attenuate lipopolysaccharide-induced acute lung injury by activating the AKT signaling pathway to reduce pyroptosis in endothelial cells [35]. These findings indirectly support our hypothesis. However, further investigations are necessary to validate the underlying biological mechanisms of FGF5. Specifically, comprehensive clinical studies should be conducted to evaluate the prognostic significance of FGF5 levels in patients with AKI. Additionally, in vitro and animal model research is needed to elucidate the intricate immunomodulatory effects of FGF5 on the development of AKI. It is crucial to fully understand how FGF5 regulates inflammatory pathways and contributes to organ damage and recovery in order to determine its potential as a therapeutic intervention for AKI. In conclusion, although there is promise regarding FGF5 as a target for treating AKI, it still requires both clinical validation and mechanistic investigation.

This study possesses several notable strengths. Firstly, we employ MR in conjunction with meta-analysis to establish causal inferences while effectively mitigating the confounding bias, thereby presenting a significant advantage over conventional observational studies. Secondly, we conduct an unprecedented exploration of 91 cellular inflammatory cytokines, offering a comprehensive overview of potential mediators for AKI. Thirdly, we unveil an innovative association between FGF5 and AKI, providing valuable insights into previously undisclosed pathogenic mechanisms. Lastly, we propose logical avenues for future research to authenticate and expand upon these findings.

However, this study also has some limitations. First, the method relies on precisely selected genetic variants as instrumental variables, and the selectivity and pleiotropy of these variants can lead to bias in the causal inference. Second, the statistical power is limited by the explanatory power of instrumental variants for exposure factors, and differences in the distribution of genetic variants across populations may limit the generalizability of the findings. In addition, the accuracy of the exposure factor measurements, publication bias, and selective reporting may affect the accuracy and reliability of the findings. Finally, the complexity of biological processes, such as the presence of multiple mediating variables and feedback loops, may affect the interpretation of MR results. Despite these challenges, studies can be carefully designed by selecting appropriate instrumental variants and statistical methods to minimize bias and improve accuracy and reliability, making MR combined with meta-analysis a powerful tool for uncovering potential causal relationships.

Conclusions

By utilizing a combination of MR and meta-analysis, this study presents innovative findings that establish a causal link between the levels of FGF5 in circulation and AKI through genetic prediction. These results suggest the potential involvement of this cytokine in the development of AKI. Future investigations should encompass clinical studies involving diverse patient populations to validate the prognostic value of FGF5.

Additionally, it is imperative to conduct cell and animal studies to authenticate the observed associations and unravel the underlying biological mechanisms connecting FGF5 with AKI. Nonetheless, this study offers fresh perspectives on the role played by cytokine mediators in AKI and proposes promising avenues for future research endeavors.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

HZ: Conceptualization, Funding acquisition, Methodology, Writing - original draft. JY: Data curation, Software, Visualization, Writing – original draft.

JH:supervision,Writing -review & editing.

Funding

The authors declare receipt of research, authorship, and publication of this article. This work was supported by Jinhua city Science and Technology Program Project (2021-3-073).

Data Availability Statement

The original contributions presented in the study are included in the article/Supplementary Material. All data used in the current study are publicly available GWAS summary data.

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